SOME OBSERVATIONS OF THE RESPIRATORY EXCHANGE OF NORMAL AND INFECTED ANIMALS, TOGETHER WITH A DESCRIPTION OF A NEW APPARATUS FOR ESTIMATING THE RESPIRATORY EXCHANGE.

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by

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SOME OBSERVATIONS OF THE RESPIRATORY EXCHANGE OF NORMAL AND INFECTED ANIMALS, TOGETHER WITH A DESCRIPTION OF A NEW APPARATUS FOR ESTIMATING THE RESPIRATORY EXCHANGE.

This work, which was carried out in the R. C. P. Laboratory, Edinburgh was originally intended to be a study of the metabolism in fever. It was found necessary to restrict the scope of the Research somewhat, but it may be well to explain my aims in taking up this work and how and why they were modified during the progress of the experiments.

My intention, then, was to study the absorption of Oxygen and the discharge of CO_2, and the effects of variation of the temperature of the environment on these processes and on the body temperature, firstly in the case of normal animals, and secondly in the case of animals whose body temperature was raised or lowered above or below the normal by inoculation with various substances bacterial and non-bacterial.

In that way I thought it might be possible to throw some light on the question as to how much the phenomena of fever as dependent on the mere increase of body temperature and how much on the infection which is its cause.

As/

As the term "Fever" is used somewhat loosely sometimes to express merely a raised body temperature, but more properly to express a well-recognised group of symptoms of which a high temperature is one of the most prominent, and which is generally dependent on bacterial infection, it may be well to state that it is in this latter sense that the term is used throughout this paper.

The high temperature which is usually a feature of Fever is a result of impairment of the Heat Regulating power of the organism or in other words an interference with the normal balance between Heat production and Heat Loss.

There has been much discussion as to whether the high temperature in Fever is due to an increase of Heat production or a diminution of Heat Loss.

In many cases there undoubtedly is an increase in Heat production. For example we often see patients with hot flushed skin and dilated peripheral vessels and even sweating freely and yet maintaining an abnormally high temperature. In these cases there is obviously an increase of Heat Loss consequently there must be a still greater increase of Heat production to maintain the high temperature. Liebermeister[1] held that the Heat Loss in patients with a raised temperature must be greater than in the normal/

normal stato and that therefore the Heat production must also be increased. He even went so far as to say that the amount of increase of Heat production corresponding to given rise of temperature could be calculated.

Senator[2] working with dogs in which a high temperature was produced by injections of pus found no material increase of CO_2 discharge and accordingly concluded that increase of Heat Production was not an essential accompaniment of Fever.

Leyden[3] made a number of observations on patients suffering from various kinds of Fevers and found the CO_2 discharge increased above the normal in the proportion (on an average) of $1\frac{1}{2}$; 1; and again Leyden and Fränkel[4] using dogs with a temperature above the normal as a result of injections of pus found a marked increase in the discharge of CO_2 .

Pflüger as a result of experiments performed by Finkler[5] on fevered animals favoured the view that increased Heat Production is an essential accompaniment of Fever. Von Noorden[6] on the other hand states that increased oxidation is not an essential accompaniment of Fever.

Whatever may be the respective values of the conclusions of these observers, it is obvious that a rise/

rise of body temperature could be brought about by either increase of Heat Production or decrease of Heat Loss or by increase of both, provided that the increase of Heat Production is out of proportion to the decrease of Heat Loss. Stress has been laid on this point by Pembrey[7]. It is a disorder of the Heat Regulation, which normally makes the one balance the other and so maintains the normal level of the body temperature, that is the cause of the rise of temperature in Fever.

Doubtless in some cases it is the alteration in Heat Production and in others the alteration in Heat Loss which is responsible for the abnormal temperature. Thus in Respiratory Exchange experiments we would expect sometimes to find an increase in the absorption of Oxygen and discharge of CO_2 and at other times no such increase. My experiments which will be detailed later go to justify this expectation.

The question of the Regulation of the body temperature in Fever is a very interesting one.

Liebermeister[8] propounded the theory that in Fever a new normal, as it were, is established (e.g. 39°C instead of the normal 37°C.) and that the organism strives to maintain this temperature varying its Heat Production and Heat Loss to meet alterations in/

in the temperature of the environment, just as it does in health.

Burdon Saunderson[9] quotes the following experiment in support of this view:

"It is possible either to raise or to depress the "temperature of a healthy person by gradually cooling "or warming the water of a warm bath in which he is "placed. If by this means his temperature is "depressed as much as $\frac{1}{3}^{o}$F. he shivers, if raised to "the same amount he perspires. Repeating the experi- "ment on a Fever patient a similar result is obtained, "with this difference, that if the temperature is, "say, 104^{o}F. he shivers at 103.7^{o} and perspires at "104.3, whereas the healthy person whose normal "temperature is 98.8^{o}F. shivers at 98.3 and sweats at "99.2.

"The explanation is that it is the change of "temperature which produces the reaction and the "direction which determines its character - shivering "if it is descending , sweating if it is ascending."

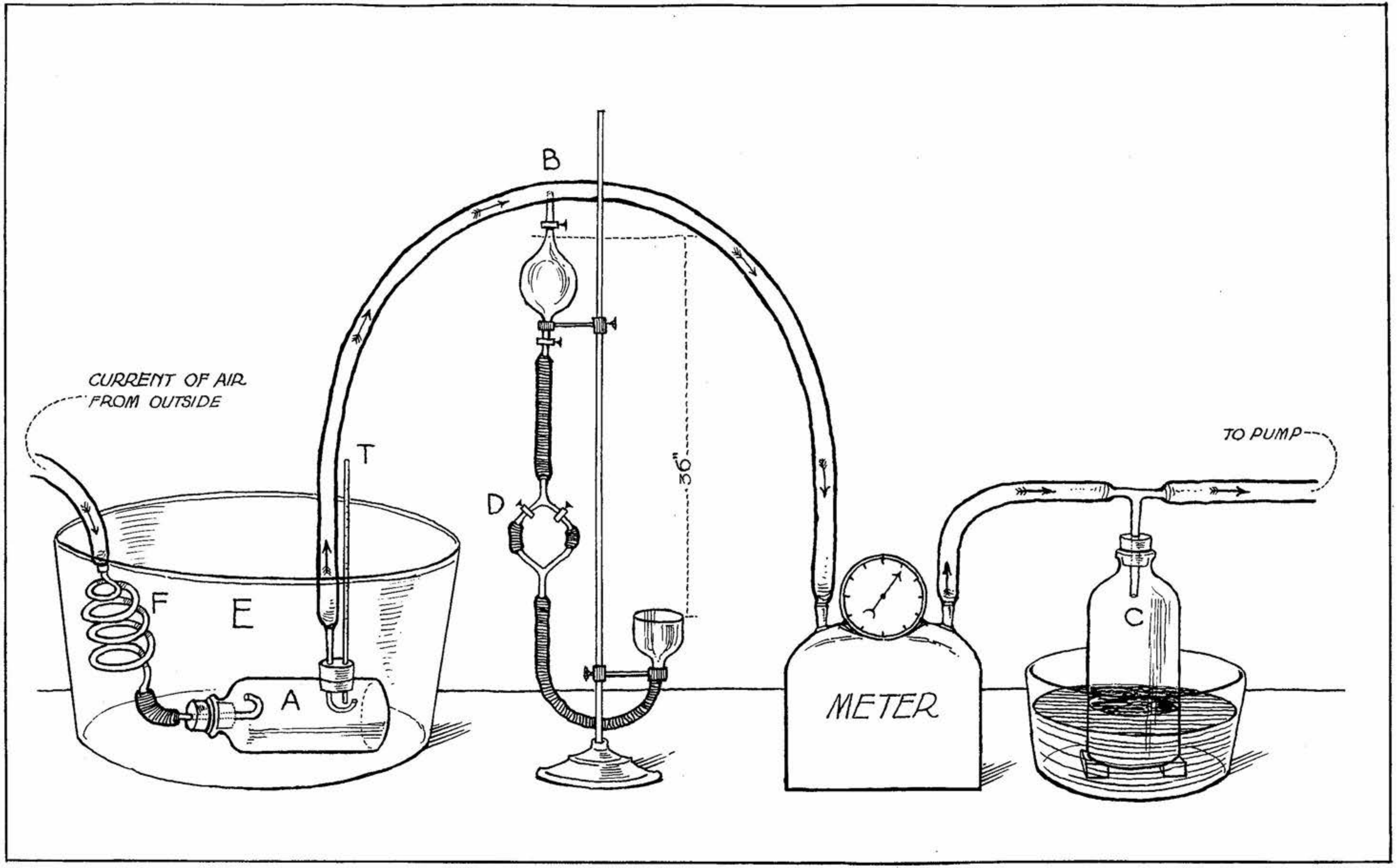
Pembrey[10] says - "Although the temperature of "a Fever patient is abnormally high the nervous "control is not absent, it is only impaired; in fact "Liebermeister held that mechanism of regulation "resembled that found in the healthy person with this "sole/

"sole difference that the mean point was 'set' at a "higher level. This view however cannot be accepted "for the characteristic of the fevered patient is the "labile state of his nervouse control over the heat "of his body; his temperature is easily raised or "lowered by disturbing conditions which would have "little or no effect upon the mean temperature of a "healthy man. The feverish patient is easily affected "by cold nervous excitement and muscular effort."

This however simply means that the patient is not so well able to maintain his temperature at the new level; it may be that he reacts in the same way as a healthy person but is unable to react to a sufficient extent to maintain the temperature as constant at its new level as it is maintained at the normal level in health.

I have thought it worth while to quote these two passages verbatim as this seems to me a very important matter in the consideration of the process of Fever and it is to this question that I have specially devoted my attention.

It is a well known fact[11] that a warm-blooded animal when the temperature of its environment is raised absorbs less O_2 and gives off less CO_2, while in cold surroundings it absorbs more O_2 and gives off more/


B
CURRENT OF AIR
FROM OUTSIDE
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more CO_2, this being evidence of, in the one case less and in the other more Heat Production. This together with alteration of its Heat Loss maintains its body temperature constant in the different surroundings.

Now I thought it would be interesting to test the effect of hot and cold environment on the body temperature and Respiratory Exchange of animals with an abnormal body temperature and to determine whether they reacted in the same way as normal animals, whether they were as well able to maintain their body temperature constant in environments of different temperatures and whether their Respiratory Exchange was affected in the same way and to the same degree as that of normal animals. The apparatus used for estimating the Respiratory Exchange was suggested by an apparatus described by Sutton[12], which itself is a modification of the method of Zuntz.

The apparatus is shown in the accompanying diagram. The animal chamber A., is a wide-mouthed glass bottle, its transparency allowing one to watch the state of activity of the animal during the experiment. The neck of the bottle is fitted with a rubber cork, perforated to admit a glass tube. At the other end there is a hole in the side of the bottle also fitted with a rubber cork. This cork admits a/

a glass tube and a thermometer T. The glass tubes are bent back as shown in the figure so that there shall not be a direct draught of air passing straight from the one to the other, but a thorough mixing of the air in the bottle as the stream of air passes through it.

Each glass tube is connected with a piece of ordinary rubber hose-tubing, the one directly, the other through the medium of a short coil of copper tubing whose use will be explained later. The hose-pipe conducts air from outside the building through the copper tube to the chamber and on from the chamber to a gas-meter and from the meter to a suction pump. The suction pump used was a simple Geissler's tube such as is described by Haldane,[13] attached to an ordinary water-tap. When put into action it sucks a current of air from outside the building through the whole system, the meter registering the rate at which the air passes.

At B. is a small hole in the hose-pipe into which a sampling tube can be tightly fitted.

All the junctions must be air-tight and to this end should be luted with some plastic material such as modeller's plasticine.

The whole system may be tested for air-tightness as/

as follows :-

A bottomless glass bottle, C., standing in a vessel of water is interposed between the meter and the suction pump as shown in the diagram. The end of the hose-pipe through which the outside air enters is then closed and the pump put into operation. A negative pressure is thus obtained throughout the system and the water consequently rises in the bottle C. The tube is then clamped between C. and the pump and the presence of a leak will be shown by the falling of the level of the water in C.

The sampling tube is a modification of that described by Haldane[14] for use in connection with his air analysis apparatus. It consists of a bulb with a 2 - way tap above it and a single-way tap below. This is attached by thick-walled rubber tubing to a mercury reservoir. By raising the reservoir the bulb and the short small bored tube leading up from it are filled with mercury. The taps above and below the bulb are then closed and the tube leading up from the bulb inserted into the hole in hose-pipe. The reservoir is then lowered and all is ready for the collection of a sample. When a sample is to be withdrawn the taps are opened, the mercury flows out of the bulb and air from the lumen/

lumen of the hose-pipe is sucked in to take its place.

Just before the bulb is completely empty of mercury the taps are again closed and the sample may be removed for analysis.

In order that the sample might be collected very slowly a tap in this case was interposed between the bulb and the reservoir and fixed in such a position that an extremely narrow channel was provided for the mercury to flow through. In this way the bulb took twenty minutes to empty of mercury, that is to say, the sample took twenty minutes to collect. As the sample, when it is to be analysed has to be driven out of the bulb by raising the reservoir and filling the bulb with mercury and as this process would take twenty minutes if the mercury went back through the same narrow channel, another route had to be provided for it, guarded by another tap which is kept closed during the collection of the sample, but opened when the sample is to be driven out. This arrangement is shown in the figure at D.

Another point about the sampling tube is that the tube connecting the bulb and the reservoir must be so long that the reservoir can be lowered more than the barometric height below the bulb. This is in order to secure that the bulb shall be emptied of mercury/

mercury at a constant rate during the whole of the twenty minutes and I am indebted for this device to Sutton's paper.[12]

The samples were analysed by Haldane's air - analysis apparatus[14]. This apparatus is fully described in the papers referred to but the principle of it is this : A sample of air is passed from the sampling tube into a graduated burette. Its volume is then noted. It is then passed into a solution of K O H till all the CO_2 is absorbed. Its volume is then measured again, the diminution in volume found being the volume of CO_2 which it had contained. The oxygen is absrobed by Pyrogallato of Potash and the vòlume again measured, the diminution in volume giving the amount of oxygen contained in the sample.

This is a most excellent and reliable apparatus, though, as I found to my cost, it takes a very great amount of practice before one can rely on one's results. Another difficulty is to obtain an accurately graduated burette. I spent two months at least sending for burettes testing them and returning them before I could obtain one sufficiently accurate. It is absolutely essential that the burette should be graduated with perfect accuracy and such a burette seems very difficult to obtain.

The/

The burette is tested by filling it with mercury inverting it and weighing out portions accurately measured according to the reading of the burette. If one has pure mercury, a constant temperature and accurate scales then any discrepancy between weight and measurement shows that the burette is inaccurate. It is a tedious process but anyone intending to use Haldane's apparatus should go through it, as an inaccurate burette leads to endless trouble.

Having obtained a satisfactory burette and perfected one's technique in the use of the instrument one finds it a most convenient and reliable apparatus for measuring the percentages of O_2 and CO_2 in the sample. A Respiratory Exchange estimation is carried out as follows :-

The animal is placed in the chamber, the cork tightly fitted on, the sampling tube, ready to take a sample, is inserted and then the whole apparatus tested for air-tightness. A stream of air through the chamber is then started and, after ten minutes or so to allow for the emptying of all the air which was in the apparatus at the commencement, a sample is taken. The rate of ventilation during the collection of the sample, as given by the meter, is noted. The sample is then analysed and the percentages of O_2 /

O_2 and CO_2 noted. Now we know the percentages of O_2 and CO_2 in the pure air entering the chamber. It is not necessary to examine a sample of the entering air if it is taken from outside the building. In the paper already quoted[14] Haldane states that the percentage of CO_2 and O_2 in outside air does not vary enough to be appreciable in an experiment of this kind. I have satisfied myself of this by repeatedly analysing samples of air which had passed through the chamber with no animal in it. Moreover several competent scientists who are in the habit of using Haldane's analysis apparatus have told me that they find the composition of outside air so invariable that they now use it as a means of testing a new burette. If a sample of ordinary outside air analysed by a new burette appears to contain unusual percentages of CO_2 and O_2, the burette will be found to be inaccurate. Knowing, then, the total amount of air entering and leaving the chamber and knowing the percentages of O_2 and CO_2 in the air before it enters and after it leaves the chamber, we know how much O_2 has been abstracted from, and how much CO_2 added to the air, by the animal in a given time; that is to say, we know how much CO_2 the animal has given off and how much O_2 it has absorbed.

Allowance/

Allowance has to be made, however, for the fact that the animal takes in more air than it gives off when the Respiratory Quotient is less than unity. A means of calculating this was very kindly suggested to me by Dr. J. S. Haldane, Reader in Physiology at Oxford University. I quote the method from his letter :-

"Pure dry air contains 79.04% of nitrogen, 20.93%
"of oxygen and 0.03% of CO_2. Owing to the Respiratory
"Quotient the nitrogen percentage is increased in the
"air passing through the meter of the apparatus.
"There may, for instance, be 79.30% of nitrogen in this.
"This would correspond in the original air not to 20.93
"but to 20.93 X $\frac{79.30}{79.04}$ = 21.00 % of oxygen in the
"air passing through the meter, the real percentage of
"absorbed oxygen being not 20.93 - 20,00 = 0.93 %
"but 21.00 - 20.00 = 1.00 %. For the CO_2 this
"correction would be inappreciable."

This will be made clearer by the following specimen calculation:-

Guinea-pig - Weight 395 grammes.

Ventilation - 115 litres per hour (calculated volume at $0^{o}C$ and 760 m.m. pressure.)

Percentage of O_2 in sample 20.43

Percentage of CO_2 in sample 0.44

∴ Percentage/

$\therefore$ Percentage of Nitrogen in sample 100 - 20.43 + 44 = 79.13.

$\therefore$ Percentage of Oxygen absorbed by animal is 20.93 $\times \frac{79.13}{79.04}$ - 20.43 = 0.52.

Percentage of CO_2 added to the air by animal is 0.44 - 0.03 = 0.41.

Respiratory Quotient = $\frac{.41}{.52}$ = .788.

O_2 absorbed by animal per hour $\frac{115}{100} \times .52 = .598$ litres.

CO_2 given off by animal per hour $\frac{115}{100} \times .41$ = .471 litres.

O_2 per hour and kilogram body weight $\frac{.598}{.395}$ = 1.513 litres = 1513 c.c.

CO_2 per hour and kilogram body weight $\frac{.471}{.395}$ = 1.193 litres = 1193 c.c.

It will be seen that though the explanation of the use of the apparatus is tedious and complicated, the use of it and the calculations necessary are simple enough, when once one has mastered the technique. The variations in temperature of the animal's environment were obtained by immersing the animal chamber in a bath of water (E in figure) and making the air pass through a short coil of copper tubing (F in figure) also immersed in the water, before reaching the chamber/

chamber. By altering the temperature of the water in the bath the temperature in the chamber could be altered as desired. The thermometer (T) inserted through the cork into the chamber gave the temperature of the air in the chamber. It was found quite easy to maintain this steadily at the temperature desired. As compared with Haldane and Pembrey's apparatus[15-16] for the estimation of Respiratory Exchange, which in many ways is probably the best for small animals, this apparatus has some advantages and some disadvantages. It has the theoretical disadvantage that it merely examines a sample of the air which has passed through the chamber whereas in their method the actual amount of CO_2 given off by the animal is weighed.

I do not think this is a real disadvantage, however, if the sample is collected slowly as described. You are then examining a continuously collected sample of the air which has passed out of the chamber during twenty minutes and this would seem to be as good as examining the whole quantity of air which has passed through the chamber in that time. The period of examination too could be lengthened if desired. It might be arranged that the sample took a whole hour to collect and if this were done you would have a measure of the Respiratory Exchange during that hour. On the other hand this method has the advantage/

advantage that the oxygen absorbed is directly estimated whereas in Haldane and Pembrey's method it is merely deduced on the assumption that the difference between the weight of H_2O and CO_2 given off by the animal and the loss of weight of the animal is entirely due to the absorption of oxygen. Doubtless this is a justifiable assumption but this method, in directly estimating the oxygen absorption has at least a theoretical advantage.

Again Haldane and Pembrey's animals are supplied with air from which all the H_2O and CO_2 have been abstracted, whereas mine are supplied with perfectly normal atmospheric air. For examining the Respiratory Exchange continuously over long periods Haldane and Pembrey's is undoubtedly the best but where, as in the case of my experiments, it is only desired to examine the Respiratory Exchange during short periods, I think the method here described is quite as reliable if not more so, and it certainly supplies a reliable alternative method if for any reason Haldane and Pembrey's is not suitable.

The following estimations of the Respiratory Exchange in normal guinea-pigs show that, by this method, similar results to those of other observers, are obtained.

Animal	Temperature of Chamber.	cc of CO_2* per hour and kilo. bodyweight	cc of O_2* per hour and kilo. bodyweight.
Guinea-pig No. 2	17.8° C.	1266	1473
" " " 4	17	934	902
" " " 7	18	902	1102
" " " 8	15.5	844	1025
" " " 9	17.5	1173	1283
" " " 10	16	871	1027
" " " 11	18	1135	1189
" " " 12	15	1269	1523
" " " 13	17	1103	1292
" " " 15	19.7	866	1094
" " " 14	18.5	785	962
" " " 16	18.7	796	1046
Maximum		1269	1523
Minimum		785	962
Average		995	1173

Note: In the case of the maximum figures the temperature of the chamber is the minimum, namely 15°C, in the case of the minimum figures the temperature is 18.5°C which is almost the maximum temperature in the series.

* All the volumes of gases given in this paper are corrected to 0°C and 760 m.m. Barometric pressure.

The figures given in Schäfer's Text Book of Physiology[17] for the Respiratory Exchange of normal guinea-pigs are as follows :-

Animal	Temperature of chamber	CO_2 per hour & kilo body-weight	O_2 per hour and kilo bodyweight	Observer
Guinea-pig	18.8°C	1.896 grammes i.e. 962 c.c.	1.612 grammes. i.e. 1125 c.c.	18 Colasanti
Guinea-pig	22	1.758 grammes i.e. 892 c.c.	1.478 grammes i.e. 1032c.c.	17 Pembrey
Guinea-pig	20	1.885 grammes i.e. 957 c.c.	1.416 grammes i.e. 988 c.c.	17 Pembrey

These tables show that the average in my series corresponds very closely with the figures given by other observers, and the variations above and below the average in the different guinea-pigs are not greater than would be expected. My figures tend to be higher than Pembrey's but it will be noticed that the temperature of the chamber was rather lower in my series than in his two cases, and, though the variations do not in all cases follow the temperature of/

of the chamber the maximum figures were obtained at the lowest temperature of the series and the minimum at almost the highest.

I think, then we may take it that the results obtained by this form of apparatus are reliable.

Unfortunately the devising and construction of this apparatus, experiments to test its efficiency and the overcoming of a great many difficulties which arose took up so much time that I found myself compelled to restrict the scope of my experiments and, instead of studying different animals under the influence of various organismal and non-organismal poisons I had to be content with experiments on guinea-pigs in the normal state and in a state of Pneumo-coccal infection.

Great difficulty was experienced in attempting to produce a rise of temperature in guinea-pigs by means of this agent. If a large dose was given the animal died very rapidly with a subnormal temperature, sometimes preceded by a rise of temperature lasting an hour or so, sometimes without any previous rise. With a small dose there would be no symptoms for several days, then a short rise lasting at most a few hours, then a fall to normal and finally death in a lethargic condition with a subnormal temperature. It/

It was easy enough to obtain material for experiments on infected animals with subnormal temperatures but very difficult to get a rise of temperature, lasting long enough for an experiment to be performed in that condition.

The cultures were made on blood agar from the heart blood of a rabbit or guinea-pig which had been injected with sputum from a case of Pneumonia. Emulsions of the living organisms made from these cultures were injected subcutaneously.

The temperature was taken in the Rectum by means of a half minute clinical thermometer, the thermometer being inserted just beyond the sphincter and held there for a minute, then pushed into the rectum for a distance of 1½ inches and held there for another minute.

Apparently the guinea-pig is so susceptible to the Pneumococcus that there is very little reaction, the animal being felled by the poison and the vitality rapidly lowered as shown by the state of extreme lethargy and low body temperature.

In this connection I should like to refer to one or two experiments which I did with the drug β-tetrahydronaphthylamine. This drug when injected into animals causes a rise of temperature. Fawcett and/

and Hale White[19] injected 0.09 gramme of this substance into a rabbit and obtained a rise of temperature. I commenced a series of experiments with this drug, which unfortunately I was unable to continue but in the two or three which were performed an interesting observation was made. Having injected rabbits with a certain dose and a rise of temperature having resulted I injected the same dose per kilo. body-weight into guinea-pigs and found a fall instead of a rise. Knowing their liability to have a subnormal temperature as a result of injection with Pneumococci I was very much interested in this result and equally so to find that a smaller dose caused a rise of temperature.

The following tables give the details.

Animal	Date	Weight	Time	Rectal Temper-ature.	CO_2 per hour & kilo.	O_2 per hour & kilo.	Remarks.
Rabbit No. 6.	12/10/09.	1850 gm.	12noon	100.4°F	408 c.c.	580 cc.	Injected at 12.25 pm. with 0.1gramme of β-tetrahydronaphthylamine i.e. 0.054 gm. perkilo body weight.
			2-45 pm.	104.7°F	523	865	
			3-23 p.m.	104.2°F	512	874	
			3-47 p.m.	103.9	501	787	
Rabbit No. 6	15/10/09.	1940 gm.	1-4 p.m.	101°F	557	644	Injected at 1-45 p.m. with 0.13gm. of the drug i.e. 0.67 g. per kilo.
			3-50 p.m.	105.1°F	850	986	
Rabbit No. 6.	29/10/09.	1970 gm.	11-8 a.m.	100.3°F	382	448	Injected at 12-15 p.m. with .15gm. of the drug i.e. .076 gm. per kilo.
			1-15 p.m.	102.9	641	863	
			2-20	103.3	656	656	
			3-15	102.7	443	609	
			5-45	101.3	388	582	

These experiments on rabbits were performed before I adopted the method of slow collection of the sample, consequently not much reliance can be placed on the figures for the Respiratory Exchange, still I give them for what they are worth. It will be noticed that in each case there is a marked rise in the Respiratory Exchange with the rise in body temperature.

These are the only experiments quoted in this paper which were performed in this fallacious manner. The figures for the body temperature are of course not affected and are reliable.

Compare these experiments now with those on guinea-pigs.

Date	Animal	Weight	Time	Rectal Temp.	CO_2 per hour & kilo.	O_2 per hour & kilo.	Respiratory Quotient	Remarks.
6/5/10	Guinea-pig No. 14.	385 gm.	3p.m.	102°F	-	-	-	
								Injected at 3 p.m. with .03 grm. of β-tetrahydronaphthylamine i.e. .077 gm. per kilo.
			3-35 p.m.	99.8				
			3-50	98.2				
			5-15	96.6				
			8-30	99.7				
			10-30	100				
31/5/10	Guinea-pig No. 14.	395 gm.	12-20p.m.	102°F	1193 c.c.	1513 c.c.	.788	
								Injected at 12-40 p.m. with .01 gm. of the drug i.e. .025 gm. per kilo.
			1-10	104.8	1506	1867	.806	
			1-40	102	-	-	-	
			2-10	101.7	1231	1490	.826	
			3-30	103	-	-	-	
			5-0	102.2	-	-	-	

These results are, of course, too fragmentary to lay any stress on, but they are interesting in this respect that, so far as they go, they show that, like Pneumococcus, this substance produces a rise of temperature in guinea-pigs in small doses and a fall in larger doses. Also that the same dose per kilo body weight causes a rise of temperature in the rabbit and a fall in the guinea-pig.

The Respiratory Exchange experiment in the guinea-pig (and those in the rabbits so far as they can be relied on) is interesting in showing a marked increase after the injection of the drug. If, as Ott and Scott[20] endeavoured to prove, the rise of temperature after injection of β-tetrahydronaphthylamine, is due to an increased combustion of Carbohydrates then one would expect to find both an increase of the Respiratory Exchange and a rise in the Respiratory Quotient both of which occurred in the experiment detailed above.

To return to the animals infected with Pneumococcus :-

The Respiratory Exchange experiments were always performed on animals in a fasting condition. Pembrey[21] has shown that four hours is a long enough period for the/

the effects of digestion to pass off but these animals had always fasted for from twelve to twenty-four hours. It was impossible always to take them at the same period for the infected animals had to be taken at a time when their temperature was in the desired phase and one could not predict accurately when this would be.

The first of the following tables shows simply a comparison of the Respiratory Exchange of the same animals in the normal and in the infected conditions at room temperature, the infection being a Pneumococcal one.

Animal	Date	Weight in grammes	Period of starvation before experiment	Temp. of chamber	Rectal Temp. immediately after collection of sample. C.	F.	cc. of CO_2 per hour & kilo bodyweight	cc. of O_2 per hour & kilo.	R. Q.*	Condition of animal	Remarks.
Guinea-pig No. 3	19/2/10	595	24 hours	19.5°C	38.2	100.8	983	1119	.87	normal	making occasional movements. -1
	21/2/10	565	24 "	16.5	40.18	104.3	962	1251	.769	infected	" "
" " 4	22/2/10	570	18 "	17	38.8	101.8	934	1064	.878	normal	sitting quietly
	23/2/10	430	20 "	16.7	39.9	103.8	1307	1663	.785	infected	" "
" " 13	6/4/10	330	24 "	17	38.7	101.7	1103	1292	.853	normal	occasional movements.
"	16/6/10	320	12 "	20	40.9	105.7	1083	1402	.772	infected	quiet.
" " 14	29/6/10	400	24 "	18.5	37.9	100.4	785	962	.818	normal	quiet
	18/7/10	420	21 "	18.7	39.8	103.8	1047	1466	.714	infected	quiet
" " 16	15/7/10	480	24 "	18.7	38.4	101.2	796	1046	.761	normal	quiet.
	22/7/10	470	12 "	19	39.95	103.9	810	1096	.739	infected	quiet.
" " 7	9/3/10	515	24 "	18	39	102.1	902	1102	.818	normal	quiet.
	13/3/10	465	12 "	14	37.4	99.4	1064	1281	.830	infected	quiet, lethargic ill-looking.
" " 9	22/3/10	390	24 "	17.5	39	102.1	1173	1283	.914	normal	making frequent but slight movem-
	24/3/10	370	24 "	17.6	30.5	86.9	554	642	.863	severe infection	very still scarcely moved. Looks very ill.
" " 10	25/3/10	440	24 "	16	38.5	101.3	871	1027	.848	normal	quiet
	29/3/10	330	24 "	16.5	37.8	100	986	1221	.807	infected	quiet
" " 12	5/4/10	315	20 "	14	38.7	101.7	1269	1523	.833	normal	quiet
	7/4/10	305	24 "	14	21.8	71.2	321	393	.818	severe infection	motionless, moribund
" " 13	6/4/10	330	24 "	17	38.7	101.7	1103	1292	.853	normal	occasional movements.
	22/6/10	280	12 "	20	37.05	98.7	1010	1298	.777	infected	quiet
	23/6/10	275	12 "	19.6	35.35	95.6	670	801	.836	severe infection	quiet.

* R. Q. "stands for Respiratory Quotient."

Of these results the first five show the normal animal as compared with the same animal in a state of Pneumococcal infection and with an abnormally high temperature. (I found the normal temperature to be in nearly every case between 101°F and 102°F, the minimum observed in my guinea-pigs when in a normal state being 100.4°F and the maximum 102.3°F. These figures agree with those given by Eyre[22] as the result of 140 observations on ten guinea-pigs.) The remainder show the normal animal as compared with the same animal in a state of Pneumococcal infection and with an abnormally low temperature. Of those with a high temperature three showed practically no change in the Respiratory Exchange as compared with the normal, two showed a well marked increase.

This is in favour of the view that in Fever there may or may not be an increase of Heat Production.

The Respiratory Quotient is in each case lower in the infected state presumably because of increased protein combustion. Of those with an abnormally low temperature two show a slight increase in the Respiratory Exchange, one shows practically no change and three show a marked diminution. In all these three cases the infection was very severe, the animal very lethargic and ill-looking, the Rectal Temperature strikingly/

strikingly below the normal. In one case the Rectal temperature reached the astonishingly low figure of $21.8^{o}C$ ($71.2^{o}F$). In this case where the animal was almost moribund the Respiratory Exchange was very much reduced. But in the cases where the infection was not so severe, although, the Rectal Temperature was distinctly below normal the Respiratory Exchange was maintained at its usual level.

Guinea-pig No. 13 is especially interesting as we can compare it in the normal state and in three stages of the infected state :

1. With a high temperature.
2. With a low temperature, but not quite overcome by the poison.
3. With a still lower temperature and a very severe infection.

We find that the Respiratory Exchange is much the same in the normal state and in the first two stages of infection but markedly diminished in the condition of severe infection.

The next series of results shows the effect on the Rectal temperature and Respiratory Exchange, of raising and lowering the temperature of the environment in the case of normal animals and of the same animals infected with Pneumococcus, and having an abnormally/

abnormally high or abnormally low Rectal temperature.

The Respiratory Exchange was first examined at Room temperature, then after the animal had been subjected to a temperature of 30°C for not less than half an hour and finally after it had been subjected to a temperature of about 10°C for not less than half an hour. That this was a long enough exposure to the high and low temperature for the effect on the Respiratory Exchange to have become constant is shown by Pembrey's experiments[23] on the Reaction Time of mammals to the temperature of their environment.

The high and low temperatures were obtained by immersing the chamber in a bath of hot water or ice and water. In this way it was easy to bring the temperature constantly to 30°C but it was more difficult to obtain exactly the same low temperature in successive experiments and the low temperature varied in the different experiments a little above and below 10°C though it was possible to maintain the temperature constant during the collection of the samples in each experiment. The temperature of the chamber moreover was not quite so low during the half hour before the collection of the sample as it was during the collection of the sample. It fell about 2°C in the half hour preceding the collection of the sample. However that/

that amount of difference is, I think, almost negligible. This of course is not quite satisfactory and if I had been able to comtinue these experiments I should certainly have had to devise some means by which a series of experiments could be done with the temperature of the chamber at exactly the same medium, high and low temperature and with exposures of equal length to these tempêratutes in each case. But by the time I had obtained the results detailed in this paper I had spent some eighteen months at the work, having so many difficulties to overcome in the construction of the apparatus and was unable to continue at it longer.

The conditions of the experiments, however, approximate sufficiently closely to the ideal, I think, to make them of value as preliminary results.

The following are tables of the results obtained.

Respiratory Exchange of normal animals in Room temperature and at a high and a low temperature.

Animal	Weight in grammes	Interval of Starvation.	Temp. of Chamber	Rectal Temp. °C	Rectal Temp. °F	cc of CO_2 per hour & kilo	cc of O_2 per hour & kilo.	R. Q.	Rise or fall in CO_2 *	Rise or fall in O_2 *	Remarks.
Guinea-pig No.2	695	24 hours	17.8°C	39	102.2	1266	1473	.76	-	-	Quiet
			30. °C	39.2	102.5	834	1044	.80	-34%	-29%	Quiet
" " 4	570	18 "	17°C	38.8	101.8	934	1064	.878	-	-	Sitting quietly, huddled together.
			30°C	39.05	102.3	763	915	.833	-18%	-14%	lying on its side most of the time,
			7.5°C	38	100.4	1907	2286	.834	+104%	+114%	a good deal of movement.
" " 7	515	24 "	18	39	102.1	902	1102	.818	-	-	Quiet
			30	38.9	102	699	854	.818	-22%	-22%	"
			9	38.9	102	1031	1250	.825	+14%	+13%	"
" " 8	425	24 "	15.5	38.4	101.1	846	1025	.825	-	-	Quiet
			30	39.2	102.3	698	857	.814	-17%	-16%	"
			7.5	38.85	101.9	1287	1569	.820	+52%	+53%	Making active movements.
" " 9	390	24 "	17.5	39	102.1	1173	1283	.914	-	-	Frequent slight movements
			30	39.1	102.4	867	819	1.05	-26%	-36%	Frequent slight movements.
			8	39.05	102.3	1294	1678	.771	+ 9%	+30%	Occasional movements
" " 10	440	24 "	16	38.5	101.3	871	1027	.848	-	-	Very little movement.
			29.5	38.8	101.8	836	920	.909	- 4%	-10%	Occasional movements.
			9.5	38.15	100.7	1152	1254	.916	+32%	+22%	Frequent slight movements.

*As compared with CO_2 given off and O_2 absorbed at Room temperature.

Normal animals (continued)

Animal	Weight in grammes	Interval of star-vation	Temp.of Chamber	Rectal Temp. °C	Rectal Temp. °F	cc of CO_2 per hour & kilo	cc of CO_2 per hour & kilo	R. Q.	Rise or fall in CO_2	Rise or fall in O_2	Remarks.
Guinea-pig No.11	355	24 hours	18°C	38.5	101.4	1135	1189	.95	-	-	Quiet.
			30	38.5	101.4	888	1122	.791	-21 %	-5 %	"
			3.5	38.1	100.6	1666	2056	.809	+46	+72 %	Active movements.
" " 12	315	20 "	15	38.7	101.7	1269	1523	.833	-	-	Quiet
			30	38.5	101.3	934	1168	.800	-26 %	-23 %	"
			8	38.65	101.6	1386	1749	.792	+ 9	+12	"
" " 13	330	24 "	17	38.7	101.7	1103	1292	.853	-	-	Occasional movements
			29.5	38.65	101.6	887	1040	.852	-19 %	-19 %	" "
			8.3	38.5	101.3	1386	1638	.846	+25	+26	Active movements at times
" " 15	250	12 "	19.7	38.5	101.3	866	1094	.791	-	-	Quiet
			30	38.75	101.7	691	-	-	-20 %	-	Quiet, O2 not estimated.
			11	38.35	101.1	1511	1814	.833	+75 %	+66 %	Quiet.
" " 14	400	24 "	18.5	37.9	100.4	785	962	.818	-	-	Quiet
			30.2	38.55	101.4	697	883	.789	-11 %	- 8 %	"
			11	38.9	102	950	1273	.746	+20 %	+32 %	Quiet, moving a little at times
" " 16	480	24 "	18.7	38.4	101.2	796	1046	.761	-	-	Quiet
			30.2	38.3	101	619	850	.720	-22 %	-18 %	" No cold experiment done.

Infected animals with abnormally high Rectal Temperature.

Animal	Weight in grammes	Interval of starvation.	Temp. of chamber	Rectal temp. °C	Rectal temp. °F	cc of CO_2 per hour & kilo.	cc of O_2 per hour & kilo	R. Q.	Rise or fall in CO_2	Rise or fall in O_2	Remarks.
Guinea-pig No.4	430	20 hours	16.7°C 30 7	39.9 40.6 39	103.8 105 102.2	1307 826 1782	1663 863 2206	.785 .957 .807	- -36 % +36%	- -42 % +32 %	Quiet " making jerky movements.
" " 13	320	12 "	20 31 10.2	40.95 40.8 40.4	105.7 105.4 104.7	1083 800 1328	1402 1009 1771	.772 .794 .750	- -26 % +22%	- -25 % +26 %	Quiet " "
" " 14	420	21 "	18.7 29.5 11	39.8 39.9 40	103.6 103.8 104	1047 750 1151	1466 1000 1579	.714 .750 .729	- - -28.4% + 8 %	- +31.8% +7 %	Quiet " Occasional movements.
" " " 16	470	12 "	19 30 9.5	39.95 39.95 40.5	103.9 103.9 104.9	810 776 1316	1096 927 1692	.739 .836 .777	- - 4 % +62 %	- -15 % +54 %	Quiet " "

Infected animals with an abnormally low Rectal Temperature.

Animal	Weight in grammes	Interval of starvation.	Temp. of Chamber	Rectal Temp. °C	Rectal Temp. °F	cc of CO_2 per hour & kilo	cc of O_2 per hour & kilo	R. Q.	Rise or fall in CO_2	Rise or fall in O_2	Remarks
Guinea-pig No.7	465	12 hours	14	37.4	99.4	1064	1281	.830	-	-	Very quiet and ill-looking.
			29.5	38.1	100.6	773	1015	.761	-26 %	-20 %	Quiet
			8	34.9	94.8	1478	1758	.840	+38 %	+37 %	"
" " 9	370	24 "	17.6	30.5	86.9	554	642	.863	-	-	Very quiet and ill-looking.
			29.5	33.3	91.9	418	450	.928	-24 %	-29 %	Lying on side moribund. Temp. of chamb. lowered to 8°C. Animal died before sample could be taken
" " 10	330	24 "	16.5	37.8	100	986	1221	.807	-	-	Occasional movements.
			30	39.4	103	769	1281*	.600*	-22 %	-0*	Quiet
			8.5	36	96.7	1325	1856	.714	+34 %	+52 %	"
" " 13	280	12 "	20	37.05	98.7	1010	1298	.777	-	-	Quiet
			30.5	38.05	100.5	760	977	.777	-24 %	-24 %	"
			12	35.25	95.5	1243	1388	.909	+19 %	+ 5 %	Moving actively part of the time
" " 13 (later stage)	275	12 "	19.6	35.35	95.6	670	801	.836	-	-	Quiet
			29.8	35.25	95.5	576	663	.868	-14 %	-17 %	quiet lying on side very ill.
			11	21	69.8	207	248	.833	-69 %	-69 %	Moribund - Died an hour afterwards.

* This looks like an error of observation.

Analysing these results we see that in the case of the normal animals the Respiratory Exchange always fell in the heat and rose in the cold but to a very variable extent.

	CO_2	O_2
Maximum Rise in Cold -	104 %	114 %
minimum Rise in Cold -	9 %	12 %
Maximum Fall in Heat -	34 %	29 %
minimum Fall in Heat -	4 %	10 %

The rise or fall in the CO_2 and O_2 was not always proportionate, in other words the Respiratory Quotient varied but no principle underlying the variations in the Respiratory Quotient is apparent.

In the case of the very large rise (104 % in the CO_2 and 114 % in the O_2) the animal was making very active movements, which would help to account for it. The infected animals with one exception always showed a fall of Respiratory Exchange in the Heat and a rise in the Cold. The exception was an animal suffering from a very severe infection (Guinea-pig No. 13) and with a very low Rectal temperature, in fact moribund. Its Respiratory Exchange fell in the Heat but fell still more in the cold and its Rectal temperature fell to the astonishing figure of 21°C in the Cold. It died an hour later so it is not to be wondered/

wondered at, that its Respiratory Exchange did not follow the usual rule.

Leaving this one out of account and setting aside one case (Guinea-pig No. 10) in which while the CO_2 fell 22 % in the Heat, the oxygen did not fall at all, and in which one must suppose there was some error of observation, we get the following for Infected animals.

		CO_2	O_2
Maximum Rise in Cold	-	62 %	54 %
Minimum Rise in Cold	-	8 %	7 %
Maximum Fall in Hot	-	36 %	42 %
Minimum Fall in Hot	-	4 %	15 %

So we see that the infected animals whether with raised or lowered Rectal temperature reacted in the same direction as the normal animals and to practically the same extent.

The Rectal Temperature of the normal animals never rose in the heat more than .8°C and only one fell as much as 1°C in the cold.

Of the infected animals with raised Rectal Temperature only one showed a tendency for the Rectal temperature to rise in the Heat and fall in the Cold; and it only rose .7°C and fell 1.6°C.

The infected animals with a low Rectal Temperature were/

were evidently less able to regulate their temperature than those with a high Rectal Temperature. Two of those were almost moribund. The Rectal Temperature of one of these rose 2.8°C in the Heat and it died in the Cold. The Rectal Temperature of the other fell 0.1°C in the Heat and fell 14.2°C in the Cold, reaching the extremely low figure of 21°C. (I have no doubt that this was a correct observation. The same thermometer gave correct results with other guinea-pigs both before and after this one. It was held in the rectum for several minutes and pushed well in but did not rise above 21°C.)

The others rose 0.7 to 1.6 in the heat and fell 2.85 to 3.4 in the cold.

The conclusions to be drawn from these experiments seem to me to be as follows :-

I. That a rise of body temperature in guinea-pigs, due to infection, is not necessarily accompanied by an increase in the absorption of oxygen and the discharge of CO_2 (which, within limits, is an indication of the amount of Heat Production).
Similarly that a fall of temperature due to infection is not necessarily accompanied by a decrease in the absorption of O_2 and discharge of CO_2. Where the infection/

infection is very severe and the temperature excessively low a fall in the amount of Respiratory Exchange takes place. This is only what one would expect - that when death is rapidly approaching and the animal lying almost motionless its metabolism will be proceeding less actively.

2. That an infected animal whether with an abnormally high or abnormally low temperature (unless very severely poisoned and in fact moribund) reacts like a normal animal, as regards its Respiratory Exchange, to change in the temperature of its surroundings, so endeavouring to keep the body temperature constant, at its new level.

That in less severe cases with a high body temperature it succeeds in keeping its temperature fairly constant while in more severe infections with a low body temperature it does not succeed so well.

This is interesting in being in support of Liebermeister's view already quoted that in Fever the temperature of the body is set at a new level and that the body aims at maintaining that new level instead of the normal one.

I am only too well aware that these experiments are too fragmentary and imperfect to have any very definite conclusions based upon them. I should have liked to follow them up and to multiply their number and/

and improve the conditions under which they were performed but this was impossible and I can only claim to have opened up an interesting line of Research and to have obtained some preliminary results which are at least suggestive and seem to indicate that it is a line worth following out.

I wish to express my very heart-felt thanks to Dr. James Ritchie, the Superintendent of the Royal College of Physicians' Laboratory of Edinburgh under whose supervision these experiments were done, both for suggesting this line of Research to me and for the constant interest he took in the progress of my work and the invaluable advice and help which he gave me.

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